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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	13

DATE MAILED: 01/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/765,060	Yu
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above, claim(s) *1-35, 45, 46, 53, and 78* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *36-44, 47-52, 54-77, and 79* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 17, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *12*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Acknowledge is made of applicants election of the following species which pertain to the elected invention of Group X, as rejoined to Groups XI and XX: trinitrophenol, ADR-ADH, BCG, VCN, proteinase K, hydrogen peroxide, hematoxylin, ethanol, TNP-470, alkylating agent, Ha-ras, p53, laser coagulation, liver and a radiation sensitizer.

It is noted that the election of BCG of claim 44 renders moot the election of VCN in claim 45.

Claims 1-79 are pending. Claims 1-35 and 78, drawn to non-elected inventions, are withdrawn from consideration. Claims 45, 46 and 53, drawn to non-elected species are also withdrawn from consideration. Claims 36-44, 47-52, 54-77 and 79 are examined on the merits.

Claim Rejections - 35 USC § 112

1.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 36-44, 47-52, 54-77 and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 recites "autologous immune response" it is unclear how the adjective "autologous" further defines "immune response".

Claim 60 is rendered vague and indefinite by defining the anti-angiogenic agent by means of a trade name.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 41, 52, 57-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

(A)As drawn to ADR-ADH as a chelator.

Claim 41 is drawn to the administration of the chelator doxorubicin adipic-dihydrazide as a chelator. However, this compound is known to be an intermediate for the conjugation of doxorubicin to an antibody or protein (Awwad et al, Cancer, Immunology and Immunotherapy, 1994, Vol. 38, pp. 23-30, reference of the I.D.S. filed, December 3, 2002). There are no teachings in the art or in the specification on how to use the claimed ADR-ADH as a chelator to facilitate the conjugation between the hapten and a tumor antigen. ADR-ADH will react with a tumor antigen, but not have further reactivity to the hapten, and further, a chelator implies non-covalent interactions, and there are no teachings regarding the function of ADR-ADH as a chelator in the specification or any art of record.

(B)As drawn to the administration of hematoxylin as a reducing agent.

Claim 52 is drawn to the method of claim 49 wherein the reducing agent is hematoxylin. The art teaches that hematoxylin undergoes autoxidation to form superoxide (Martin et al, Archives of biochemistry and Biophysics, 1987, Vol. 255, pp. 329-336). There is no further teachings in the specification or any art of record to support the use of hematoxylin as a reducing agent.

(C)As drawn to the administration of an anti-neoplasm agent in conjunction with TNP linked to carbodiimide, oxidizing or reducing agents. Claims 57-67 are drawn to methods wherein anti-neoplasm agents, anti-angiogenic agents, alkylating agents, oncogene inhibitors and tumor suppressor genes or proteins are administered in conjunction with a combination comprising a hapten, an oxidizing or reducing agent and a protein denaturing agent. Said combination is chemically reactive with respect to all the components, the hapten, the oxidation/reduction agent

and the protein denaturing agent. There are no specific teachings or examples in the specification to support the notion that other proteins or chemicals would be inert to the combination. It would be reasonable to assume that an alkylating agent would be susceptible to reaction with the TNP attached to a carbodiimide group, which had not yet reacted with a protein on the tumor cell. It would be reasonable to assume that any protein agent such as an oncogene inhibitor or a tumor suppressor gene would also be susceptible to the hapten attached to the carobidiimide as well as to the oxidation/reduction agents and the protein denaturation agent.

Given the teachings of the art with regard to the reactivity of the above compounds and the lack of teachings in the specification, one of skill in the art would be subject to undue experimentation in order to carry out the claimed methods.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 36, 38, 43, 44, 70, 71, 73 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dima et al (Laser therapy, 1990, Vol. 2, pp. 153-160) in view of Krosl et al (Cancer research, 1996, Vol. 56, pp. 3281-3286) and Berd (US 5,290,551).

Claim 36 is drawn to a method for treating neoplasm in a mammal comprising in situ administration of an effective amount of a hapten and a coagulation agent or treatment, whereby an immune response is generated against the neoplasm and the neoplasm is treated. Claim 38

embodies the method of claim 36 wherein the hapten is trinitrophenol. . Claim 43 embodies the method of claim 36 wherein the method further comprises an immune response potentiator. Claim 44 species the immune response potentiator is BCG. Claim 70 embodies the method of claim 36, wherein the coagulation treatment is laser coagulation. Claim 71 specifies that the immune response generated by the method of claim 36 comprises a humoral and/or cellular immune response. Claim 73 embodies the method of claim 36 for the treatment of solid tumors.

Dima et al teach a method of treating a neoplasm in a mammal comprising laser therapy as a coagulation treatment, in combination with the immune response potentiator, BCG, and a Photofrin II as a photosensitizer. Dima et al do not teach the administration of a hapten.

Krosly et al teach that photodynamic therapy kills tumor cells by damage to the tumor vasculature and by the induction of a strong tumor localized acute inflammatory reaction which results in conditions for the processing and presentation of tumor antigens by antigen presenting cells resulting in the development of tumor specific immunity by means of a T-cell response (introduction, first paragraph). Thus, Krosyl et al teach the induction of cellular immune response.

Berd et al teaches that modification of tumor cells with the hapten results in the induction of an immune response exemplified by the infiltration of the tumor with CD-8 T-cells against the modified tumor (column 6, lines 24-27) thus teaching the induction of a cellular immune response. Berd teaches that trinitrophenol can be used a said hapten (column 3, lines 38-39).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the hapten trinitrophenol as an addition to the method taught by Dima et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Krosyl et al on the induction of specific antitumor immune responses by photodynamic therapy and the teachings of Berd on the induction of tumor infiltrating lymphocytes by the administration of a trinitrophenol-modified tumor vaccine. One of

skill in the art would be motivated to combine the methods in order to take advantage of the increased immune response generated by photodynamic therapy in the induction of specific anti-tumor cellular immunity.

7. Claims 36-38, 43, 44, 70, 71, 73-75 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dima et al (Laser therapy, 1990, Vol. 2, pp. 153-160) and Krosl et al (Cancer research, 1996, Vol. 56, pp. 3281-3286) and Berd (US 5,290,551) as applied to claims 36, 38, 43, 44, 70, 71, 73 and 79 above, and further in view of Skobelkin et al (Laser therapy, 1991, Vol. 3, pp. 169-175). Claim 37 embodies the method of claim 36 wherein the mammal is a human. Claims 74 and 75 specify a solid tumor larger than 108 cells and a solid tumor from about 5 X 109 to about 1011 cells.

The combination of Dima et al and Krosyl et al and Berd et al render obvious the limitations of claims 36, 38, 43, 44, 70, 71, 73 and 79 for the reasons set forth above. Berd teaches the induction of a cellular immune response against the tumor by the administration of a hapten modified tumor vaccine to humans. Neither Dima et, nor Krosyl et al teach the upregulation of the immune system in humans after laser therapy.

Skobelkin et al teach that after laser therapy the total force of the immune response in oncologic patients is increased. This is evidenced by an increase in the number of T-helper cells and a decrease in the number of T-suppressor cells (page 173, second column, last paragraph). It appears that the number of the tumor cells within the treated patients is within the claimed range of cells recited in claims 74 and 75.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to carrying out the method taught by Dima et al and Krosyl et al and Berd on a human.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Skobelkin et al on the upregulation of the total immune response in human patients having cancer after laser therapy. One of skill in the art would be

motivated to do so as the immune response induced by the laser seems to have the same effect on humans as on laboratory animals.

8. Claims 36, 38, 43, 44, 47-51, 70, 71, 73, 79 rejected under 35 U.S.C. 103(a) as being unpatentable over Dima et al (Laser therapy, 1990, Vol. 2, pp. 153-160) and Krosl et al (Cancer research, 1996, Vol. 56, pp. 3281-3286) and Berd (US 5,290,551) as applied to claims 36, 38, 43, 44, 70, 71, 73 and 79 in section 4 above, and further in view of Gomer et al (WO 98/40105) and Todryk et al (Journal of Immunology, 1999, Vol. 163, pp. 1398-1408) and Molloy et al (Journal of Experimental Medicine, 1994, Vol. 180, pp. 1499-1509). Claim 47 embodies the method of claim 36 further comprising the administration of a coagulation lysing agent to the neoplasm.

Claim 47 embodies the method of claim 36 further comprising the administration of a coagulation lysing agent. Claim 48 specifies that the coagulation lysing agent is proteinase K. Claim 49 embodies the method of claim 36 wherein the coagulation agent is a combination comprising an oxidizing or reducing agent and a protein denaturing agent. Claim 50 specifies that the combination of the method of claim 49 is formulated in a single pharmaceutical composition of in separate pharmaceutical compositions. Claim 51 embodies the method of claim 49 wherein the oxidizing agent is hydrogen peroxide.

The combination of Dima et al and Krosyl et al and Berd et al render obvious the limitations of claims 36, 38, 43, 44, 70, 71, 73 and 79 for the reasons set forth above. Neither Dima et al nor Krosyl et al nor Berd teach the administration of proteinase K or a coagulation lysing agent nor a combination of an oxidizing agent or reducing agent with a protein denaturing agent.

Gomer et al teach that photodynamic therapy induces the expression of heat shock genes (page 3, lines 4-6). Gomer et al teach that photochemical reaction induced by photosensitizers

and laser light produces reactive oxygen species which damage subcellular targets and that photodynamic therapy is used to treat solid tumors (page 10, lines 21-28).

Todryk et al teach that expression of the heat shock protein, hsp70, on tumors results in increased numbers of tumor infiltrating lymphocytes comprising T-cells and dendritic cells (page 1401, first column last paragraph) and that the immune response is tumor specific (page 1401, under the heading "Protection conferred by hsp70 expression is tumor specific...". Todryk et al teach that tumor cell lysates induce the maturation of dendritic cells (page 1402, under the heading "tumor cell lysates...") and that induction of hsp expression during necrotic cell death results in the accumulation of dendritic cells and other immune cells within tumors (page 1407, last paragraph). Todryk et al teach that tumor cell death from necrosis versus apoptosis, can induce potent antitumor immunity through the expression of the heat shock protein, hsp70 (page 1404, second column, under the heading "Discussion").

Masafumi et al teach that proteinase K is a protein denaturing agent.

Molloy et al teach that hydrogen peroxide is an inducer of cellular necrosis.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to carry out the method rendered obvious by the combination of Dima et al and Krosyl et al and Berd with the additional administration of proteinase K and hydrogen peroxide.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Gomer et al on the induction of heat shock genes and oxygen radicals by laser therapy; the teachings of Molloy et al on the induction of necrosis by hydrogen peroxide; the teachings of Todryk et al on the importance of heat shock proteins released by necrotic tumor cells in the induction of an antitumor response; and the teachings of what is well know in the art as exemplified by Masafumi et al that proteinase K is a cellular lysing agent and a protein denaturing agent. One of skill in the art would be motivated to combine proteinase k with hydrogen peroxide because the art teaches that proteinase K can lyse cells, and

hydrogen peroxide can cause cellular necrosis, thereby further augmenting the necrotic damage to the tumor cells inflicted by the laser therapy, said necrotic damage as taught by Todryk to be important in the generation of potent anti tumor immunity.

9. Claims 36, 38, 43, 44, 47-50, 54-56, 70-73, 76, and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dima et al (Laser therapy, 1990, Vol. 2, pp. 153-160) and Krosl et al (Cancer research, 1996, Vol. 56, pp. 3281-3286) and Berd (US 5,290,551) and Gomer et al (WO 98/40105) and Todryk et al (Journal of Immunology, 1999, Vol. 163, pp. 1398-1408) as applied to claims 36, 38, 43, 44, 47-50, 70, 71, 73, 79 in section 6 above, and further in view of Lin et al (Journal of Gastroenterology and Hepatology, 1997, Vol. 12, pp. S319-S328).

Claims 54-56 drawn to the method of claim 49 wherein the protein denaturing agent is ethanol. Claim 72 specifies that the neoplasm is a liver neoplasm. Claim 76 is drawn to the method of claim 36 wherein the hapten and coagulation agent is administered to the neoplasm via injection.

Dima et al (Laser therapy, 1990, Vol. 2, pp. 153-160) and Krosl et al (Cancer research, 1996, Vol. 56, pp. 3281-3286) and Berd (US 5,290,551) and Gomer et al (WO 98/40105) and Todryk et al (Journal of Immunology, 1999, Vol. 163, pp. 1398-1408) and Masafumi et al (EP 240191) render obvious claims 36, 38, 43, 44, 47-50, 70, 71, 73, 79 for the reasons set forth above. Neither Dima et al, Krosl et al, Berd, Gomer et al, Todryk et al, Masafumi et al nor Molloy et al teach alcohol as a denaturing agent, nor the administration to the neoplasm via injection of the coagulation agent and hapten.

Lin et al teaches the direct injection of ethanol into liver tumors can cause coagulation necrosis of said tumor (page S324, first column, first paragraph under "Local injection therapy" and second column, under the heading "External radiation"). Lin et al also teaches radiation doses that are compatible with external radiation to treat hepatocellular carcinoma.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute ethanol for proteinase K and inject both the ethanol and hapten directly into the tumor.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Lin et al on the necrosis induced by direct injection into liver tumors, and the teachings of Todryk et al on the desirability of inducing tumor necrosis in order to generate anti tumor immunity resulting in tumor infiltrating lymphocytes and the teachings of Berd et al on the generation of tumor infiltrating lymphocytes by haptenized tumor antigens. One of ordinary skill in the art would be motivated to inject the hapten directly into the tumor in addition to the ethanol because the art teaches direct ethanol injection and by combining the hapten with the ethanol a high concentration of hapten can be delivered directly to the tumor thereby avoiding dilution in the bloodstream and reaction t non-specific sites.

10. Claims 36, 38, 43, 44, 70, 71, 73, 77 and 79 rejected under 35 U.S.C. 103(a) as being unpatentable over Dima et al (Laser therapy, 1990, Vol. 2, pp. 153-160) and Krosl et al (Cancer research, 1996, Vol. 56, pp. 3281-3286) and Berd (US 5,290,551) as applied to claims 36, 38, 43, 44, 70, 71, 73 and 79 above, and further in view of Brien et al (Lasers in surgery and Medicine, 1992, Vol. 12, pp. 313-317). Claim 77 embodies the method of claim 36 wherein the hapten and coagulation agent are administered to the neoplasm in combination with a surgical procedure.

The combination of Dima et al, Krosyl et al and Berd render obvious claims 36, 38, 43, 44, 70, 71, 73 and 79 for the reasons set forth in section 6 above. Neither of the aforesaid references specifically teach the administration of the hapten and coagulation agent in combination with surgery.

Brien et al teach that laser excision and sterilization of the wound augments the anti-tumor response. Brien et al teaches that the animal with laser extirpated tumors had a higher rate of

tumor recurrence in comparison to those animals which were treated with a scalpel excision as a greater amount of normal tissue surrounding the tumor was excised by scaple technique

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the hapten at the time of laser surgery.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Brien on the induction of the immune response by laser excision and on small pieces of tumor which were left behind due to less than optimal technique with laser excision. One of skill in the art would be motivated to apply the hapten at the time of laser surgery to augment the immune response against any small pieces of tumor which were inadvertently left behind.

11. Claims 36, 38-40, 42, 43, 44, 70, 71, 73 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dima et al (Laser therapy, 1990, Vol. 2, pp. 153-160) and Krosl et al (Cancer research, 1996, Vol. 56, pp. 3281-3286) and Berd (US 5,290,551) as applied to claims 36, 38, 43, 44, 70, 71, 73 and 79 above, and further in view of Lisowski et al (Journal of Immunological Methods, 1972, Vol. 1, pp. 341-352). Claim 39 embodies the method of claim 36 further comprising a facilitating agent. Claim 40 embodies the method of claim 39 wherein the facilitating agent is a chemical linking agent. Claim 42 specifies that the chemical linking agent is carbodiimide.

Dima et al, Krosyl and Berd render obvious the embodiments of claims 36, 38, 43, 44, 70, 71, 73 and 79 for the reasons set forth above. Neither of the afforesaid references teaches carbodiimide as a linking agent. Berd teaches TNP chemically linked to tumor cells.

Lisowski et al teaches carbodiimide to link TNP to antibodies.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to chemically link TNP to the tumor cell by means of carbodiimide as a linker.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Lisowski et al on the linking of TNP to antibodies by means of carbodiimide. It is reasonable to assume that carbodiimide will therefore link TNP to proteins on the tumor cell.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
December 30, 2002